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Dated 22 November 2004

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THE PATENT OFFICE

29 OCT 2003

NEWPORT

The Patent Office

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1. Your reference

101272

2. Patent application number

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P01/7700 0.00-0325192.3

29 OCT 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number (if you know it)

7822448003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

METHOD OF USE

5. Name of your agent (if you have one)

Philip French

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca
Global Intellectual Property
PO Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG

Patents ADP number (if you know it)

8179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description	15
Claim(s)	06
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

Date

Authorised Signatory

28/10/2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Helen Dixon - 01625 517301

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METHOD OF USE

The present invention relates to a novel use of sulphonamide compounds of Formula (I) as inhibitors of both acetyl CoA(acetyl coenzyme A):diacylglycerol acyltransferase and acetyl CoA:cholesterol acyl transferase and to their use in the treatment of type II diabetes, insulin resistance, impaired glucose tolerance and obesity.

A key enzyme in triglyceride synthesis is acyl CoA:diacylglycerol acyltransferase (DGAT), which is found in the microsomal fraction of cells. DGAT catalyzes the final reaction in the glycerol phosphate pathway, considered to be the main pathway of triglyceride synthesis in cells. The enzyme is also believed to catalyze the final step of the monoacylglycerol pathway, found predominantly in enterocytes of the small intestine. In both pathways, DGAT facilitates the joining of a diacylglycerol with a fatty acyl CoA, resulting in the formation of triglyceride. Although it is unclear whether DGAT is rate-limiting for triglyceride synthesis, it catalyzes the only step in the pathway that is committed to producing this type of molecule [Lehner & Kuksis (1996) Biosynthesis of triacylglycerols. Prog. Lipid Res. 35: 169-201].

In 1998, a DGAT gene was identified from sequence database searches because of its similarity to acyl CoA:cholesterol acyltransferase (ACAT) genes. [Cases *et al* (1998) Identification of a gene encoding an acyl CoA:diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. Proc. Natl. Acad. Sci. USA 95: 13018-13023]. DGAT activity has been found in many mammalian tissues, including rat adipocytes, differentiated 3T3-L1 adipocytes, enterocytes of the small intestine and mammary gland. DGAT is active in both skeletal and heart muscle, where triglycerides serve as stores of fatty acids for oxidative metabolism.

Because of the previous lack of molecular probes, little is known about the regulation of DGAT. DGAT is known to be significantly up-regulated during adipocyte differentiation. As DGAT acts at an important branch point in the glycerolipid synthetic pathway, its activity may also be regulated in accordance with the metabolic state of the cell. Several studies have reported that hormones influence DGAT activity and the enzyme may be post-translationally regulated by a tyrosine kinase.

Studies in gene knockout mice has indicated that modulators of the activity of DGAT would be of value in the treatment of type II diabetes and obesity. DGAT knockout (*Dgat*^{-/-}) mice, are viable and capable of synthesizing triglycerides, as evidenced by normal fasting serum triglyceride levels and normal adipose tissue composition. *Dgat*^{-/-} mice have less

adipose tissue than wild-type mice at baseline and are resistant to diet-induced obesity. This is not due to decreased caloric intake in these animals. However, metabolic rate is ~20% higher in *Dgat*^{-/-} mice than in wild-type mice on both regular and high-fat diets [Smith *et al* (2000) Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking DGAT.

5 Nature Genetics 25: 87-90]. Increased physical activity in *Dgat*^{-/-} mice partially accounts for their increased energy expenditure. The *Dgat*^{-/-} mice also exhibit increased insulin sensitivity and a 20% increase in glucose disposal rate. Leptin levels are 50% decreased in the *Dgat*^{-/-} mice in line with the 50% decrease in fat mass.

When *Dgat*^{-/-} mice are crossed with *ob/ob* mice, these mice exhibit the *ob/ob*
10 phenotype [Chen *et al* (2002) Increased insulin and leptin sensitivity in mice lacking acyl CoA:diacylglycerol acyltransferase J. Clin. Invest. 109:1049-1055]. When *Dgat*^{-/-} mice are crossed with *Agouti* mice a decrease in body weight is seen with normal glucose levels and 70% reduced insulin levels compared to wild type, *agouti* or *ob/ob/ Dgat*^{-/-} mice. Food intake is the same but activity is increased. Expression changes in brown and white adipose tissue
15 are consistent with activation of the leptin pathway. These changes are absent in *ob/ob* mice.

Transplantation of adipose tissue from *Dgat*^{-/-} mice to wild type mice confers resistance to diet-induced obesity and improved glucose metabolism in these mice [Chen *et al* (2003) Obesity resistance and enhanced glucose metabolism in mice transplanted with white adipose tissue lacking acyl CoA:diacylglycerol acyltransferase J. Clin. Invest. 111: 1715-
20 1722].

Recently a DGAT enzyme without sequence homology to previously identified DGAT genes was isolated from the fungus *Mortierella rammaniana*. A mammalian gene family related to this fungal DGAT has been identified. One member of this family, DGAT2, has been cloned and characterised [Cases *et al* (2001) Cloning of DGAT2, a second mammalian
25 diacylglycerol acyltransferase, and related family members. J. Biol. Chem. 276:38870-38876.]. DGAT2 has no sequence homology with DGAT1 but shares some homology with the monoacylglycerol acyltransferase (MGAT) family [Yen *et al* (2002) Identification of a gene encoding MGAT1, a monoacylglycerol acyltransferase. Proc. Natl. Acad. Sci. USA

residual activity in *Dgat*^{-/-} tissues (DGAT1^{-/-}) is relatively low even when low MgCl₂ concentrations are used. Recent evidence suggests that the overt DGAT activity found in hepatocytes is associated with DGAT2.

Acyl-CoA:cholesterol acyltransferase (ACAT) enzymes catalyze the synthesis of cholesterol esters from free cholesterol and fatty acyl-CoAs thereby participating in regulating the concentration of cellular free sterols. The cholesterol ester products of ACAT reactions can be stored in cytosolic droplets, which may serve to protect cells from the toxicity of free cholesterol. In macrophages, the accumulation of these droplets results in the formation of 'foam cells', a hallmark of early atherosclerotic lesions [Brown & Goldstein (1983) Annu. Rev. Biochem. 52:223-261.]. In hepatocytes and enterocytes, cholesterol esters can be incorporated into apolipoprotein B-containing lipoproteins for secretion from the cell and hence ACAT enzymes play key regulatory roles in intestinal cholesterol absorption and in hepatic synthesis and secretion of lipoproteins.

In 1993, Chang and co-workers succeeded in cloning a human ACAT gene, now known as ACAT1 [Chang *et al* (1993) Molecular cloning and functional expression of human acyl-coenzyme A:cholesterol acyltransferase cDNA in mutant Chinese hamster ovary cells. J. Biol. Chem. 268: 20747-20755]. The cloning of ACAT1 led to the identification of a second ACAT gene, ACAT2 [Anderson *et al.*(1998) Identification of a form of acyl-CoA:cholesterol acyltransferase specific to liver and intestine in nonhuman primates. J. Biol. Chem. 273: 26747-26754; Cases *et al.*(1998) ACAT-2, a second mammalian acyl-CoA:cholesterol acyltransferase. Its cloning, expression, and characterisation. J. Biol. Chem. 273: 26755-26764; Oelkers *et al* (1998) Characterisation of two human genes encoding acyl coenzyme A:cholesterol acyltransferase-related enzymes. J. Biol. Chem. 273: 26765-26771]. ACAT1 has many hydrophobic regions, consistent with it being an integral membrane protein. Most of the seven transmembrane domains have sequences that are highly conserved among other ACAT enzymes. As these regions are not conserved in DGAT enzymes, it has been hypothesized that these regions bind cholesterol in the membrane.

ACAT1 mRNA is expressed ubiquitously in mammalian tissues. Expression levels of ACAT1 are highest in the adrenal glands, macrophages, and sebaceous glands; and in humans is also detectable in liver and intestinal epithelial cells. ACAT1 expression has also been detected in human atherosclerotic lesions.

ACAT1 appears to be regulated primarily by posttranslational mechanisms and is allosterically activated by the binding of cholesterol or oxysterols.

The ACAT2 cDNA encodes a protein with greater than 40% identity to human ACAT1. ACAT2 is also a hydrophobic protein with multiple transmembrane domains. ACAT activity is found primarily in the endoplasmic reticulum. The active site for ACAT2 is located on the luminal side of the endoplasmic reticulum membrane, whereas the active site for

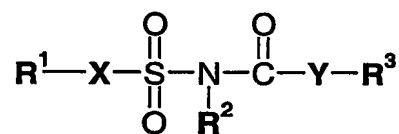
5 ACAT1 is oriented toward the cytosol. The ACAT2 sequence contains many of the same motifs found in ACAT1.

ACAT2 is expressed primarily in the liver and small intestine. In humans, nonhuman primates and mice, ACAT2 appears to be the major ACAT in the small intestine. ACAT2 also appears to be the predominant ACAT expressed in the liver of adult nonhuman primates and

10 mice.

International patent application, publication number, WO 94/26702, describes a group of sulphonamide compounds, as ACAT inhibitors, with utility in the treatment of hypercholesterolemia and atherosclerosis. We have surprisingly found that these compounds are also inhibitors of DGAT and thus of utility in the treatment of type II diabetes and obesity.

15 Thus, according to the first aspect of the invention there is provided the use of a compound of Formula (I)



Formula (I)

20 wherein

X and Y are independently selected from: oxygen, sulphur and $(-\text{CR}^a\text{R}^b-)_n$; wherein:

n is an integer of from 1 to 4 and

R^a and R^b are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, hydroxy, C_{1-6} alkanoyloxy, C_{3-12} cycloalkyl and optionally substituted phenyl or R^a and

25 R^b together form a C_{5-12} spirocycloalkyl or a carbonyl;

with the proviso that at least one of X and Y is $(-\text{CR}^a\text{R}^b-)$, and with the further proviso

phenyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C₁₋₄alkoxycarbony or $-(CH_2)_pNR_4R_5$ wherein p is 0 or 1, and R^4 and R^5 are independently selected from hydrogen or C₁₋₄alkyl;

(b) naphth-1-yl or naphth-2-yl wherein the naphthyl group is optionally substituted with from 1

5 to 3 substituents independently selected from

phenyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C₁₋₄alkoxycarbony or $-(CH_2)_pNR_4R_5$ wherein p , R^4 and R^5 are as defined above;

(c) arylC₁₋₆alkyl;

10 (d) C₁₋₂₀alkyl or C₁₋₂₀alkenyl; or

(e) adamantyl or a C₃₋₁₂cycloalkyl

R^2 is hydrogen, a C₁₋₈alkyl or benzyl;

or pharmaceutically acceptable salt, pro-drug or solvate thereof in the manufacture of a medicament for the treatment of type II diabetes and/or obesity.

15 According to a further feature of the first aspect of the invention there is provided a method of treatment, in a warm-blooded animal, of type II diabetes and/or obesity comprising the administration of a therapeutically (including prophylactically) effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a
20 pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically effective salt, pro-drug or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier for the treatment of type II diabetes and/or obesity.

According to a further feature of the first aspect of the invention there is provided the use of a compound of Formula (I) in the manufacture of a medicament for the inhibition of
25 both acetyl CoA(acetyl coenzyme A):diacylglycerol acyltransferase and acetyl CoA:cholesterol acyl transferase.

According to a further feature of the first aspect of the invention there is provided a method of treatment, in a warm-blooded animal, by the inhibition of both acetyl CoA(acetyl coenzyme A):diacylglycerol acyltransferase and acetyl CoA:cholesterol acyl transferase
30 comprising the administration of a therapeutically (including prophylactically) effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically effective salt, pro-drug or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier for the inhibition of both acetyl CoA(acetyl coenzyme A):diacylglycerol acyltransferase and acetyl CoA:cholesterol acyl transferase.

In the present specification, unless otherwise indicated, an **alkyl** group is a saturated chain having 1 to 20 carbon atoms which may be linear or branched. Examples of alkyl groups include: methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-undecyl, n-dodecyl, n-hexadecyl, 2,2-dimethyldodecyl, 2-tetradecyl, and n-octadecyl groups.

The term "**alkenyl**" refers to a carbon chain having 1 to 20 carbon atoms having from 1 to 3 double bonds. Examples of alkenyl include: ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl.

The term "**aryl**" refers to phenyl or naphthyl.

The term "**halo**" refers to fluoro, chloro, bromo or iodo.

The term "**cycloalkyl**" refers to a saturated carbocyclic ring containing between 3 and 12 carbon atoms, preferably between 3 and 8 carbon atoms. Examples of cycloalkyl include: cyclopentyl, cyclohexyl, cyclooctyl, tetrahydronaphthyl, adamant-1-yl and adamant-2-yl.

The term "**spirocycloalkyl**" refers to bicyclic saturated carbon rings containing between 5 and 12 carbon atoms wherein one carbon atom is common to both rings, Examples of spirocycloalkyl include: spirocyclopropyl, spirocyclobutyl, spirocyclopentyl and spirocyclohexyl.

The term "**treatment**" refers to both treatment and prevention.

Examples of **C₁₋₈alkoxy** include methoxy, ethoxy, n-propoxy, t-butoxy, and pentyloxy; examples of **C₁₋₆alkanoyl** include formyl, ethanoyl, propanoyl or pentanoyl, examples of **arylC₁₋₆alkyl** include benzyl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl, 2-phenylbutyl, 3-phenylbutyl, benzhexyl, 2,2-diphenylethyl and 2,3-diphenylbutyl.

the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

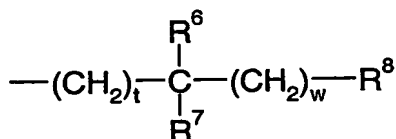
The invention also relates to any and all tautomeric forms of the compounds of the
5 different features of the invention that possess the property of treating type II diabetes and/ or obesity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of treating
10 type II diabetes and/ or obesity.

Preferred compounds of Formula (I) are those wherein any one of the following apply:

(i) R^1 and R^3 are selected from either of the following:

- (a) R^1 is phenyl or phenyl disubstituted in the 2,6-positions and R^3 is phenyl or is phenyl disubstituted in the 2,6-positions;
- 15 (b) each of R^1 and R^3 is phenyl disubstituted in the 2,6-position,
- (c) R^1 is phenyl disubstituted in the 2,6-positions and R^3 is phenyl trisubstituted in the 2,4,6-positions;
- (d) R^1 is 2,6-bis(1-methylethyl)phenyl and R^3 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl,
- 20 (e) one of R^1 and R^3 is the group



wherein

t is 0 to 4;

w is 0 to 4 with the proviso that the sum of t and w is not greater than 5;

- 25 R^6 and R^7 are independently selected from hydrogen or C_{1-6} alkyl, or when R^6 is hydrogen, R^7 can be selected from the groups defined for R^8 ; and R^8 is phenyl optionally substituted with from 1 to 3 substituents selected C_{1-6} alkyl C_{1-6} alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C_{1-4} alkoxycarbonyl, or $-(CH_2)_pNR^4R^5$ wherein p , R^4 and R^5 are as defined above.

- (ii) one of R^1 and R^3 is phenyl, and more preferably wherein one of R^1 and R^3 is substituted phenyl, and still more preferably wherein one of R^1 and R^3 is phenyl disubstituted in the 2,6-positions.
- (iii) both R^1 and R^3 are phenyl disubstituted in the 2,6-positions
- 5 (iv) R^1 is phenyl disubstituted in the 2,6-position and R^3 is trisubstituted in the 2,4,6 - positions.
- (v) R^1 is 2,6-bis(1-methylethyl)phenyl; and R^3 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.

According to a further feature of the invention there is provided the use of the following
10 preferred group of compounds, or pharmaceutically-acceptable salt, pro-drug or solvate thereof:

- (I) X is selected from oxygen, sulfur and $(-CR^aR^b-)_n$;
Y is selected from oxygen, sulfur and $(-CR^aR^b-)_n$, with the proviso that at least one of X or Y is $(-CR^aR^b-)_n$ wherein n is an integer of from 1 to 4 and R^a and R^b are
15 independently selected from hydrogen, C_{1-6} alkyl, optionally substituted phenyl, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkanoyloxy and C_{3-12} cycloalkyl, or R^a and R^b taken together form a carbonyl or C_{3-10} spirocycloalkyl;
 R^1 is selected from optionally substituted phenyl, C_{1-10} alkyl and C_{3-10} cycloalkyl;
 R^2 is hydrogen;
20 R^3 is selected from optionally substituted phenyl, C_{1-10} alkyl, C_{3-8} cycloalkyl, optionally substituted phenoxy with the proviso that only if X is $(-CR^aR^b-)_n$ can R^1 be optionally substituted phenoxy and only if Y is $(-CR^aR^b-)_n$ can R^3 be optionally substituted phenoxy, and with the further proviso that at least one of R^1 and R^3 is optionally substituted phenyl or phenoxy.

- 25 (II) X is oxygen;
Y is $(-CR^aR^b-)_n$ wherein n is an integer of from 1 to 2;
 R^1 is optionally substituted phenyl;
 R^2 is hydrogen;

(III) X is oxygen;

Y is $(-CR^aR^b)_n$ wherein n is an integer of from 1 to 4 and R' and R" are each independently hydrogen, alkyl, alkoxy, halogen, hydroxy, acyloxy, cycloalkyl, phenyl optionally substituted or R' and R" together form a spirocycloalkyl or a carbonyl;

R¹ and R³ are independently selected from

(a) phenyl or phenoxy wherein the phenyl or phenoxy group is optionally substituted with 1 to 5 substituents independently selected from

phenyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C₁₋₄alkoxycarbony or $-(CH_2)_pNR_4R_5$ wherein p is 0 or 1, and R⁴ and R⁵ are independently selected from hydrogen or C₁₋₄alkyl;

(b) naphth-1-yl or naphth-2-yl wherein the naphthyl group is optionally substituted with from 1 to 3 substituents independently selected from

phenyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C₁₋₄alkoxycarbony or $-(CH_2)_pNR_4R_5$ wherein p, R⁴ and R⁵ are as defined above;

(c) arylC₁₋₆alkyl;

(d) C₁₋₂₀alkyl or C₁₋₂₀alkenyl; or

(e) adamantyl or a C₃₋₁₂cycloalkyl

R² is hydrogen, a C₁₋₈alkyl or benzyl;

Particularly preferred compounds for use in the method according to the present invention are wherein the compound is selected from:

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis[1-methylethyl)phenyl ester

Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

- Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
 Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl
]benzeneacetamide,
- 5 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl
]benzeneacetamide-sodium salt,
 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfo
 nyl]carbamate,
 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-
- 10 methylethyl)phenyl]methyl]sulfonyl]carbamate-sodium salt,
 Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid trans-[(2-phenylcyclopropyl)-carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
- 15 Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- 20 Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
- 25 Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester.

Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

or a pharmaceutically acceptable salt, pro-drug or solvate thereof.

In therapeutic use as agents for treating of diabetes the compounds of Formulas (I) or pharmaceutically acceptable salts, pro-drugs or solvates thereof are administered to the patient at dosage levels of from 250 to 3000 mg per day. For a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 5 to 40 mg/kg of body weight per day. The specific dosages employed, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I). Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
 - b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
 - c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
 - d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
 - e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).
- 10 An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl
- 15 esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic

20 cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give

25 alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic for

organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Compounds for use in the method of the invention can be prepared as described in

- 5 International Patent Application, WO 94/26702, the contents of which are incorporated herein by reference.

The use of compounds of Formula (I) are provided as medicaments for the treatment of diabetes and/or obesity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a
10 pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents,
15 emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of
20 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the
25 composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene
30 glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

The compounds described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or

treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus pharmacotherapy may include the following main categories of treatment:

- 5 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
- 3) Insulin sensitising agents including PPAR γ agonists (for example pioglitazone and rosiglitazone);
- 10 4) Agents that suppress hepatic glucose output (for example metformin).
- 5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
- 6) Agents designed to treat the complications of prolonged hyperglycaemia;
- 7) Anti-obesity agents (for example sibutramine and orlistat);
- 15 8) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
- 20 9) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
- 10) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors);
- 25 antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and
- 11) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. corticoids).

ASSAYS

ACAT

- The ability of compounds to inhibit ACAT can be measured using an *in-vitro* test described in Field & Salone (1982) *Biochemica et Biophysica*, 712, 557-570. The test assesses the ability of a test compound to inhibit the acylation of cholesterol by oleic acid by measuring the amount of radiolabeled cholesterol oleate formed from radiolabeled oleic acid in a tissue preparation containing rat liver microsomes.

DGAT

- The ability of compounds to inhibit DGAT can be measured as described in Coleman (1992) *Methods in Enzymology* 209, 98-102.

EXAMPLE 1

- The inhibitory activity of sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester against DGAT1, DGAT2 and ACAT was measured in rat and human liver microsomes. DGAT1 and DGAT2 can be distinguished since DGAT1 is not active at high magnesium concentrations (concentrations of 50mM or higher) whilst DGAT2 retains its activity at high magnesium concentrations.
- The results obtained, expressed as the concentration of inhibitor at which 50% of the enzyme activity is inhibited, i.e. the IC_{50} , are as follows:

Rat liver microsomes -

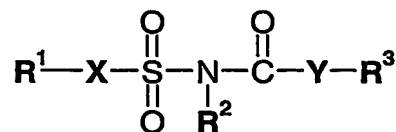
	IC_{50} (μM)
DGAT1 and DGAT2	3.41
DGAT2(100mM Mg)	2.28
ACAT	1.03

25 Human liver microsomes -

	IC_{50} (μM)
DGAT1 and DGAT2	7.95
DGAT2(100mM Mg)	3.03
ACAT	5.67

CLAIMS:

1. The use of a compound of Formula (I)



Formula (I)

X and **Y** are independently selected from: oxygen, sulphur and $(-\text{CR}^a\text{R}^b-)_n$; wherein:

n is an integer of from 1 to 4 and

R^a and **R^b** are each independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, hydroxy, C₁₋₆alkanoyloxy, C₃₋₁₂cycloalkyl and optionally substituted phenyl or **R^a** and **R^b** together form a C₅₋₁₂spirocycloalkyl or a carbonyl;

with the proviso that at least one of **X** and **Y** is $(-\text{CR}^a\text{R}^b-)_n$ and with the further proviso that when **X** and **Y** are both $(-\text{CR}^a\text{R}^b-)_n$ and **R^a** and **R^b** are hydrogen and **n** is 1, then **R¹** and **R³** are both aryl;

R² is hydrogen, a C₁₋₈alkyl or benzyl;

R¹ and **R³** are independently selected from

(a) phenyl or phenoxy wherein the phenyl or phenoxy group is optionally substituted with 1 to 5 substituents independently selected from

phenyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C₁₋₄alkoxycarbony or $-(\text{CH}_2)_p\text{NR}_4\text{R}_5$ wherein **p** is 0 or 1, and **R⁴** and **R⁵** are independently selected from hydrogen or C₁₋₄alkyl;

(b) naphth-1-yl or naphth-2-yl wherein the naphthyl group is optionally substituted with from 1 to 3 substituents independently selected from

phenyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C₁₋₄alkoxycarbony or $-(\text{CH}_2)_p\text{NR}_4\text{R}_5$ wherein **p**, **R⁴** and **R⁵** are as defined above;

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2. The use according to claim 1 wherein R^1 is phenyl.

3. The use according to claim 2 wherein R^1 is phenyl disubstituted in the 2,6-positions.

5 4. The use according to claim 1 wherein R^3 is phenyl.

5. The use according to claim 4 wherein R^3 is phenyl disubstituted in the 2,6-positions.

6. The use according to claim 1 wherein each of R^1 and R^3 is phenyl.

10

7. The use according to claim 6 wherein each phenyl is disubstituted in the 2,6-positions.

8. The use according to claim 1 wherein R^1 is phenyl disubstituted in the 2,6-positions and R^3 is phenyl trisubstituted in the 2,4,6-positions.

15

9. The use according to claim 1 wherein R^1 is 2,6-bis(1-methylethyl)phenyl and R^3 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.

10. The use according to claim 1 wherein:

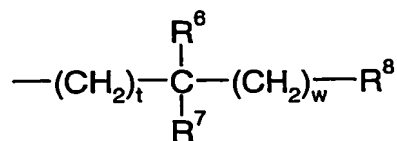
20 (a) R^1 is phenyl or phenyl disubstituted in the 2,6-positions and R^3 is phenyl or is phenyl disubstituted in the 2,6-positions;

(b) each of R^1 and R^3 is phenyl disubstituted in the 2,6-position,

(c) R^1 is phenyl disubstituted in the 2,6-positions and R^3 is phenyl trisubstituted in the 2,4,6-positions;

25 (d) R^1 is 2,6-bis(1-methylethyl)phenyl and R^3 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl,

(e) one of R^1 and R^3 is the group



wherein

30 t is 0 to 4;

w is 0 to 4 with the proviso that the sum of t and w is not greater than 5;

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R^6 and R^7 are independently selected from hydrogen or C_{1-6} alkyl, or when R^6 is hydrogen, R^7 can be selected from the groups defined for R^8 ; and R^8 is phenyl optionally substituted with from 1 to 3 substituents selected C_{1-6} alkyl C_{1-6} alkoxy, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, C_{1-4} alkoxycarbonyl, or $-(CH_2)_pNR^4R^5$ wherein p , R^4 and R^5 are as defined above.

11. The use according to claim 1 wherein

X is oxygen;

10 Y is $(CR^aR^b)_n$ wherein

n is an integer of from 1 to 4 and

R^a and R^b are each independently hydrogen, C_{1-6} alkyl, optionally substituted phenyl, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkanoyloxy, cycloalkyl, or R^a and R^b taken together form a carbonyl or C_{3-10} spirocycloalkyl;

15 R^1 is selected from optionally substituted phenyl, C_{1-10} alkyl or C_{3-10} cycloalkyl;

R^2 is hydrogen;

R^3 is selected from optionally substituted phenyl, C_{1-10} alkyl, C_{3-8} cycloalkyl and optionally substituted phenoxy.

20 12. The use according to claim 1 wherein

X is oxygen;

Y is $(CR^aR^b)_n$ wherein n is an integer of from 1 to 2;

R^1 is optionally substituted phenyl;

R^2 is hydrogen;

25 R^3 is selected from optionally substituted phenyl, optionally substituted phenoxy,

C_{1-10} alkyl, and C_{3-10} cycloalkyl;

R^a and R^b are independently selected from hydrogen, C_{1-6} alkyl, optionally substituted phenyl, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkanoyloxy, cycloalkyl, or R^a and R^b taken together form a carbonyl or a spirocycloalkyl.

13. The use according to claim 1 wherein the compound is selected:

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis[1-methylethyl)phenyl ester,

10 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

15 Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

2. 6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl] benzeneacetamide,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl] benzeneacetamide-sodium salt.

20 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl]carbamate-sodium salt,

Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

- Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
5 Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,
10 Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(11-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
15 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
20 Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester.

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Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

or pharmaceutically acceptable salt, pro-drug or solvate.

14. The use according to claim 1 wherein the compound is:

15 sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

or pharmaceutically acceptable salt, pro-drug or solvate.

15. The use according to any one of the preceding claims wherein the use is the

20 manufacture of a medicament for the treatment of type II diabetes.

16. The use according to any one of the preceding claims wherein the use is the

manufacture of a medicament for the treatment of obesity.

25 17. The use according to any one of the preceding claims wherein the use is the manufacture of a medicament for the treatment of insulin resistance.

18. The use according to any one of the preceding claims wherein the use is the manufacture of a medicament for the treatment of impaired glucose tolerance.

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